

CardioSEAL® Septal Occlusion System
Summary of Safety and Probable Benefit

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SUMMARY OF SAFETY AND PROBABLE BENEFIT

1. General Information

Device Generic Name: Transcatheter Cardiac Occlusion Device

Device Trade Name: CardioSEAL® Septal Occlusion System

Applicant's Name and Address: Nitinol Medical Technologies, Inc.
27 Wormwood Street
Boston, Mass. 02210

Humanitarian Device Exemption (HDE) Number: H990011

Date of Humanitarian Use Device Designation: August 4, 1999

Date of Panel Recommendation: Not Applicable (Refer to Section 12 for discussion)

Date of Good Manufacturing Practices Inspection: May 27, 1999

Date of Notice to the applicant: February 1, 2000

2. Indications for Use

The CardioSEAL Septal Occlusion System is authorized by Federal (USA) law as a Humanitarian Use Device for use in the following indication only:

The CardioSEAL Septal Occlusion System is indicated for the closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy.

Cryptogenic stroke is defined as a stroke occurring in the absence of potential phanerogenic cardiac, pulmonary, vascular or neurological sources. Conventional drug therapy is defined as a therapeutic INR on oral anticoagulants.

The effectiveness of this device in this indication has not been demonstrated.

3. Device Description

The CardioSEAL Septal Occlusion System consists of two primary components:

- The CardioSEAL, which is constructed of a metal (MP35N) framework to which polyester fabric is attached, and

- The Delivery Catheter, a coaxial polyurethane catheter designed specifically to facilitate attachment, loading, delivery and deployment of the CardioSEAL to the defect.

4. Contraindications

Presence of thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the defect is gained.

Active endocarditis, or other infections producing a bacteremia.

Patients whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate size sheath.

Patients whose defect is too small to allow the 11 F sheath to cross the defect.

Anatomy in which the CardioSEAL size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.

Patients with coagulation disorders who are unable to take antiplatelet or, anticoagulant therapy.

Patients with known hypercoagulable states.

Patients with an intra-cardiac mass or vegetation.

5. Warnings and Precautions:

See Warnings and Precautions in the final labeling (Information for Use).

6. ADVERSE EVENTS

6.1 Observed Adverse Events:

In a 292 patient multi-center High Risk study, 35 patients underwent closure of a PFO to prevent neurological injury. Six (6) patients had failed conventional drug therapy as evidenced by a recurrent stroke and 29 were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy (9); a medical or occupational contraindication to anticoagulation (17); could not tolerate anticoagulation (2); and presence of a thrombus in the right atrium (1).

One patient died of lung cancer while in the study. Eighteen (18) patients have completed a 12 month follow-up visit and five patients completed a 24 month visit.

A total of 44 adverse events were recorded among the 35 patients enrolled in the study for closure of their PFO. These adverse events were classified as Serious (4), Moderately

Serious (16), Not Serious (23), or Unknown Seriousness (1) and were linked to either the device, the implant procedure, the catheterization procedure, or other causes, such as a pre-existing condition. Of these 44 adverse events, 7 events were definitely, probably or possibly related to the device, the implant procedure, or the catheterization. All 7 of these events were classified as moderately serious (Table 1).

Adverse Events – Table 1		PFO (n=35)
	Moderately Serious	
	Early Event*	Late Event**
Device Related		
Transient Neurological symptoms	2	0
Implant Procedure Related		
None	0	0
Catheterization Procedure Related		
ST elevation	1	0
Brachial plexus injury	1	0
Rash	1	0
Pseudoaneurysm at vascular access site	1	0
Tachycardia	1	0

* = Early event is ≤ 30 days from implant. Total =1 early event.

** = Late event is > 30 days from implant. Total =0 late events.

In this study, fractures of the framework have been reported in 9 out of 35 implanted patients. The risk of fracture appears to be related to the size of the Occluder selected relative to the size of the heart chamber. There have been two reports of palpitations which were considered possibly related to device arm fracture. In both cases, they were classified as not serious.

6.2 Potential Adverse Events:

Placement of the CardioSEAL involves using standard interventional cardiac catheterization techniques. Complications commonly associated with these procedures include, but are not limited to:

- Air Embolus
- Allergic dye reaction
- Anesthesia reactions
- Apnea
- Arrhythmia
- Death
- Fever
- Headache / Migraines
- Hematoma and/or Pseudoaneurysm including blood loss requiring transfusion

Hypertension; Hypotension
Infection including Endocarditis
Perforation of Vessel or Myocardium
Stroke / Transient Ischemic Attack
Thromboembolic events
Valvular regurgitation.

6.3 Observed Device Malfunctions:

There were no reports of device malfunctions in this PFO population. However, there were 4 device malfunctions in a supporting cohort of patients with atrial level defects. These malfunctions included: one report of a kink in the delivery system, identified during the device placement; one report of a difficult release, the device was subsequently not used; one report of a device which did not open and the device was subsequently not used; and one report of difficulty advancing the device through the pod resulting from the physician modifying the delivery system. There were no clinical sequelae associated with any of these device malfunctions.

7. Alternative Practices and Procedures

Alternative treatments for PFO's that have failed conventional drug therapy include surgical closure.

8. Marketing History

The CardioSEAL Septal Occlusion System has received the CE mark for marketing in Europe. Since 1997 approximately 1600 devices have been sold in the European Community, Latin America, and certain Pacific Rim countries. The CardioSEAL has been used for the treatment of a variety of defects including VSDs.

The CardioSEAL has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

9. Summary of Preclinical Studies

9.1 Biocompatibility Testing

Biocompatibility testing of the implant and delivery system was shown to be acceptable by the following tests which were performed in accordance with the provisions of the ISO 10993-1 and Good Laboratory Practice (GLP) Regulations, 21 CFR 58:

Hemolysis	Cytotoxicity
Systemic Toxicity	Pyrogenicity
Intracutaneous Toxicity	Sensitization

Additional testing of the CardioSEAL included a 7-day Muscle Implant test and an Ames Mutagenicity Assay. The delivery system was also tested for Thromboresistance, Coagulation: Plasma Recalcification Time and Complement Activation. The results of this additional testing found that the implant material was non-toxic and non-mutagenic and the delivery system material was non-thrombogenic and does not activate complement.

9.2 Bench Testing

9.2.1 CardioSEAL – Bench Testing

1. Chemical analysis – MP35N wire

A chemical analysis was conducted to verify the material composition for all of the components of the permanent implant, specifically the MP35n, polyester fabric, solder, polyester suture, and platinum wire. All of these materials were tested and met their raw material specifications.

2. Mechanical Properties – MP35N wire

Testing was conducted to determine conformance of the MP35N wire to specifications and the corrosion resistance of the wire.

a) Tensile strength/Elongation

Tensile strength and elongation was tested on 124 MP35N wire samples (60 as received and 64 annealed). All samples met the specifications for these characteristics.

b) Corrosion Resistance

To evaluate the susceptibility of the CardioSEAL to stress corrosion cracking, 27 spring arm subassemblies were subjected to static deflections in simulated body fluids. Nine samples were exposed to these conditions out to 6, 9 and 12 months. Scanning electron microscope analysis of the test samples found no evidence of stress corrosion cracking after an exposure of up to 12 months.

3. Mechanical Testing – CardioSEAL

A summary of the bench testing conducted to evaluate the performance of the CardioSEAL is provided in Table 2.

Table 2: Summary of CardioSEAL Testing

Samples Tested		Specification	
Fatigue Testing:			
Accelerated Life Testing (Springarm)	N=48 (40mm)	Must withstand 10 yrs. Equivalent (pediatric heart rate) of <i>in vitro</i> fatigue cycle testing with no fractures.	No fractures occurred in 630 million cycles.
Other Mechanical Testing:			
Arm/Body Joint Strength	N= 14	10 lbs min	Mean = 25.66lbs S.D. 2.02lbs
Ball/Body Joint Strength	N=21	8 lbs min	Mean = 10.21lbs S.D. = 0.74lbs
Arm/Fabric Strength	N=30	1 lb min	Mean = 4.23lbs S.D. 0.70lbs
Dislodgement Resistance	N=10 (17mm)	Force required to pull an occluder out of a circular hole (50% of the size of the occluder) must be 38 grams minimum.	17mm = Mean = 169.7g S.D. 13.07g
	N=20 (40mm)		40mm= Mean = 54.10g S.D. = 3.70g
MRI Compatibility			
MRI Compatible	5 Implants	MR safe up to 1.5 Tesla	Non-ferromagnetic Generated artifact < the size of the implant with 1.5 Tesla

A finite element analysis (FEA) was also performed to compare the springback of the model with the laboratory springback testing, determine the stresses (static and dynamic) during the loading cycle and deployment, and compare the model's fatigue prediction with spring arm fatigue test data.

9.2.2 Delivery Catheter - Bench Testing

To demonstrate the strength of the bonded joints and their ability to resist failure, tensile testing was performed on a minimum of 10 samples for each of the bonded locations. The results found that the strength of each of the bonded joints exceeded the test specification.

9.2.3 CardioSEAL Septal Occlusion System - Bench Testing

A summary of the bench testing conducted to evaluate the performance of the CardioSEAL occluder loaded on the delivery catheter is provided in Table 3.

Table 3: Summary of CardioSEAL Septal Occlusion System Testing

Load and Deployment			
Minimum Side Length	17mm N=136 23mm N=88 40mm N=120	17mm: 10.4 mm min. 23mm: 14.0 mm min. 40mm: 24.4mm min.	17mm: Mean= 2.54mm SD=0.61mm 23mm: Mean= 16.42mm S.D. = 0.55mm 40mm: Mean=27.98mm S.D.=0.69mm
Force into Loader	17mm N=17 23mm N=11 40mm N=15	5 lbs max (applies to all sizes)	17mm: Mean = 0.93lbs S.D. = 0.35lbs 23mm: Mean = 1.14lbs S.D. = 0.36lbs 40mm: Mean = 1.11lbs. S.D.=0.43lbs.
Force into Pod	17mm N= 17 23mm N=11 40mm N=15	6 lbs max (applies to all sizes)	17mm: Mean= 1.43 lbs S.D. = 0.46lbs 23mm: Mean= 1.74lbs S.D. = 0.61lbs 40mm: Mean=2.46lbs. S.D.=0.58lbs.
Force out of Pod	17mm N= 17 23mm N=11 40mm N=15	8 lbs max (applies to all sizes)	17mm: Mean= 1.33lbs S.D. = 0.49lbs 23mm: Mean= 1.64lbs S.D. = 0.30lbs 40mm: Mean=2.61lbs S.D.=0.62lbs
Springback gap	17mm N= 68 23mm N=44 40mm N=60	After being subjected to a loading and deployment cycle, the distance between the proximal and distal sides must be ≤ 4 mm. (applies to all sizes)	17mm: Mean = 0.25mm S.D. = 0.40mm 23mm: Mean= 0.015mm S.D. = 0.098mm 40mm: Mean=0.04mm S.D.=0.28mm
Ball to Ball Strength	N=30	6 lbs min (applies to all sizes)	Mean= 9.22lbs S.D. = 0.68lbs

9.3 Sterility and Shelf Life Qualification Studies

The method of sterilization for both the CardioSEAL and delivery system is 100% ETO. The product may be sterilized no more than twice and is validated to achieve a SAL of 10^{-6} using method C of the International Document #ISO 11135, 1994 (adopted by the Committee for the Advancement of Medical Instrumentation.).

To support a 4 year shelf life, the sterility and integrity of CardioSEAL and delivery catheters, aged out to 4 years (real-time plus accelerated aged) was tested. This involved testing both the packaging and the device.

Shipping tests in accordance with the ASTM D4169, ISTA 1A tested the packaging of the CardioSEAL and delivery catheters. All packages were found intact without evidence of physical damage. Fifteen packages each of CardioSEAL devices and delivery catheters were burst tested and found to be within the test specification.

Sterility testing was conducted on 6 samples each of the CardioSEAL and delivery catheter. All samples were found to be sterile. Bond strength and functionality testing were conducted on 5 to 20 samples real time and accelerated aged out to 4 years and exposed to shipping stresses. All test results indicate that the product performs within specification and that sterility is maintained over a period of four years.

9.4 Animal Testing

Following successful initial acute studies, three chronic animal studies were conducted to evaluate the CardioSEAL using both sheep and dog models. Explants occurred at the following timepoints: 2 weeks, 30 days, 90 days, 6 months, 1 year, and 2 years. Atrial septal defects were created either via blade septostomy or Brockenbrough followed by balloon dilation. In the first study, oversized devices were placed in freshly created defects, which resulted in thrombosis and a device arm fracture. It was later confirmed that devices implanted in freshly created defects had higher levels of protein deposition and thrombosis.

The next two studies were conducted in both the sheep and dog model with defects created a minimum of 2 weeks prior to device implantation. These both resulted in an acceptable histological response. One arm fracture occurred at 30 days in a device, which did not appear to be appropriately placed within the ASD. Friction lesions were noted acutely near the suture coil location of arms not yet healed to the septal wall surface; these healed over time. The 3 month, 6 month, 1 year, and 2 year explants showed good fibrous tissue overgrowth and endothelialization with no recent thrombosis or arm fractures.

10. CLINICAL STUDIES:

Study Design/Objective: The multi-center clinical trial conducted by Children's Hospital, Boston, Massachusetts, is a prospective, non-randomized trial studying the use of the CardioSEAL® Septal Occlusion system to close a variety of hemodynamically significant cardiac defects (e.g., fenestrated fontans, ventricular septal defects, atrial septal defects). The risks of surgical closure for the patients enrolled in this trial are sufficient to justify the known and potentially unknown risks of transcatheter closure with the CardioSEAL device. The study (referred to as the High-risk study) is ongoing and is summarized below. Data from patients undergoing PFO closure, who had failed conventional drug therapy as evidenced by a recurrent stroke, was extracted from this study as well as patients who were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy ; a medical or occupational contraindication to anticoagulation; could not tolerate anticoagulation ; and presence of a thrombus in the right atrium.

Patient Entry: Patients were eligible for enrollment in the High risk study if they had a defect(s) of sufficient size to require closure, but were considered to be at high risk for surgical closure, due to either complex medical or cardiac disease. An independent peer review group determined whether a patient should be enrolled into the trial based on the following criteria:

- the patient had a type of defect that was technically difficult or impossible to close surgically, such that the surgical risks were sufficient to justify the known and potential unknown risks of the device, or
- the patient's overall medical condition was such that the surgical risks were sufficient to justify the known and potential unknown risks of the device.

Methods: After enrollment, patients underwent cardiac catheterization. Position and size of the defect were confirmed by angiography. A hemodynamic assessment was performed pre-implant, and after test occlusion of the defect with a balloon. When these data suggested that the defect contributed to unfavorable hemodynamics and was feasible for transcatheter closure, device placement proceeded. Patients received aspirin, 1mg/kg/day, rounded to the nearest half tablet of 80 mg size, for at least six months following the procedure.

Patients were seen for follow up assessments as described in Table 4:

	Pre-Implant	Pre-D/C	1 month F/U	2 month F/U	6 month F/U	24 month F/U
Cardiac HX/PE	X	X	X	X	X	X
Chest X-Ray	X	X	X	X	X	
Fluoroscopy				X		X
Echo/Doppler	X	X	X	X	X	X
Clinical Status Evaluation	X	X	X	X	X	X
EKG (rhythm)	X	X	X	X	X	X

Primary Endpoints:

Clinical Status Scale

A 6-category ordinal scale was used to measure clinical status. The scale takes values from 0 to 5, and was constructed so that an improvement by one category would be clinically relevant.

The Clinical status scale consists of seven different classes representing important aspects of overall cardiac and medical status: right to left shunt, left to right shunt, risk for systemic emboli, hemodynamic compromise not due to shunt, arrhythmia, elevated pulmonary vascular resistance, and medical illness. The condition most closely related to a patient's indication for device closure is identified, and the patient is placed in the lowest possible category according to criteria for that class.

All of the patients undergoing device placement for PFO closure to prevent neurological injury are evaluated using the criteria in Table 5 for patients with systemic emboli. A trivial or no residual leak status was considered the same as having no intracardiac potential for emboli. Embolic events, presumed or confirmed to be due to emboli include, both transient or permanent events resulting in symptoms.

Clinical Status Scale - Table 5						
Category	0	1	2	3	4	5
Systemic embolic	NA	Recurrent embolic events, on Coumadin	Recurrent embolic events, but no anticoagulation	Single embolic events	Potential for embolic event	No intra-cardiac potential for emboli

A deceased patient is rated as -1 on the Clinical Status Scale.

Additionally an assessment of the echocardiographic closure status was made at each time point both at the evaluating facility, and by an unaffiliated core laboratory. Residual flow was assessed using Doppler color flow mapping, and graded using the following guidelines:

"Trivial" to "Absent": barely detectable or no detectable residual color flow through the defect. If flow is present, it is a single color flow jet, well-circumscribed, with a proximal jet width measuring less than 1 mm in diameter in all views.

"Small": single color flow jet, well-circumscribed, and measuring 1-2mm (maximal proximal width) in all views in infants and children weighing less than 20 kg, or between 1 and 3 mm in diameter in larger children and adults.

"More than small": single color flow jet, well-circumscribed, measuring greater than 2 mm in diameter in all views in infants and children weighing less than 20 kg, or greater than 3 mm in diameter in all views in larger children and adults.

Results: At the time the PFO data was analyzed, 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke and 29 patients who were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy (9); a medical or occupational contraindication to anticoagulation (17); could not tolerate anticoagulation (2); and presence of a thrombus in the right atrium (1) were enrolled in the study for PFO closure. Enrollment occurred at four investigational sites.

Among the 6 patients treated with a CardioSEAL device who had failed conventional drug therapy as evidenced by a recurrent stroke, there were 3(50%) males and 3 (50%) females. The age of the patients ranged from 35.4 years to 60.7 years, with a median age of 48.8 years.

Among the 29 patients treated with a CardioSEAL device who were at risk of a neurologic injury, there were 14(48.3%) males and 15 (51.7%) females. The age of the patients ranged from 5.3 years to 73.2 years, with a median age of 34.7 years.

Device placement was successful in all 35 patients in whom an implant was attempted. A single device was implanted in each patient. Device sizes included: (6) 23mm, (9) 28mm, (18) 33mm and (2) 40mm device. All of the implanted devices remained stable throughout the follow-up period. None of the devices embolized or were explanted.

Table 6A reflects the number of patients observed within each clinical status category at each visit for the 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke.

Timepoint	-1	0	1	2	3	4	5	Uncertain	Missing	Not Due
Initial	0	0	6	0	0	0	0	0	0	0
Discharge	0	0	0	0	0	2	3	1	0	0
1 Month	0	0	0	0	0	1	4	0	1	0
6 Month	0	0	0	0	0	0	2	1	3	0
12 Month	0	0	0	0	0	1	4	1	0	0
24 Month	0	0	0	0	0	0	0	0	1	5

Table 6B reflects the number of patients observed within each clinical status category at each visit for the 29 patients who were at risk of a neurologic injury.

Clinical Status by Lesion Table 6B										
	Category									
Timepoint	-1	0	1	2	3	4	5	Uncertain	Missing	Not Due
Initial	0	0	9	3	16	1	0	0	0	0
Discharge	0	0	1	0	1	8	16	3	0	0
1 Month	0	0	0	1	0	5	17	3	3	0
6 Month	0	0	0	0	0	4	16	3	0	6
12 Month	1	0	0	0	0	1	7	4	1	15
24 Month	0	0	0	0	0	0	5	0	2	22

Table 7A reflects the number of patients observed within each Echo Closure category at each visit for the 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke.

Echo Closure Status - Table 7A						
	Category					
	None-Trivial	Small	Greater than small	Uncertain	Missing	Not due
Initial	0	2	0	4	0	0
Discharge	1	1	0	4	0	0
1 Month	1	1	0	2	2	0
6 Month	3	0	0	1	2	0
12 Month	4	1	0	0	1	0
24 Month	0	0	0	0	1	5

Table 7B reflects the number of patients observed within each Echo Closure category at each visit for the 29 patients who were at risk of a neurologic injury.

Echo Closure Status – Table 7B						
	Category					
	None-Trivial	Small	Greater than small	Uncertain	Missing	Not due
Initial	7	13	2	7	0	0
Discharge	21	5	0	3	0	0
1 Month	17	1	0	4	7	0
6 Month	19	1	0	2	1	6
12 Month	8	0	0	4	2	15
24 Month	5	0	0	0	2	22

11. Conclusions Drawn from the Studies

The pre-clinical studies indicate that the CardioSEAL Septal Occlusion System is biocompatible and has the appropriate physical and performance characteristics for its intended use, as stated in the labeling.

The clinical data generated from the High-risk study at Children's Hospital, Boston, Massachusetts indicates patients will not be exposed to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of alternative forms of treatment.

The preclinical studies and the clinical data from the High-risk study provide reasonable assurance of the safety and probable benefit of the CardioSEAL Septal Occlusion System when used in accordance with its labeling.

12. Panel Recommendations

A Circulatory System Devices Panel advisory meeting was not held to discuss this device. However, a general Panel meeting was held on October 24, 1997, where a lengthy discussion of clinical requirements for this category of devices, i.e., occlusion devices intended to treat congenital heart disease, took place. Based on a review of these recommendations and the data in the HDE, it was determined that a Panel meeting was not necessary for this device.

12. FDA Decision

CDRH determined that, based on the data submitted in the HDE, the CardioSEAL Septal Occlusion System will not expose patients to an unreasonable risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval on _____.

13. Approval Specifications

Indications for Use: See the Instructions for Use (Attachment 1)

Hazards to Health from Use of the Device: See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, and ADVERSE EVENTS in the Instructions for Use (Attachment 1)